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(54) Title: NOVEL PHARMACEUTICAL COMPOSITIONS FOR ANTIHISTAMINIC-DECONGESTANT COMBINATION AND METHOD OF MAKING SUCH COMPOSITIONS

(57) Abstract: The present invention relates to pharmaceutical compositions of antihistamine-decongestant combination. Specifically the invention relates to bilayered tablet formulation comprising antihistaminic decongestant combination. More specifically present invention relates to the novel polymorph of fexofenadine or pharmaceutically accepted salts thereof, with at least one decongestant in the form of bilayered tablet. The preferred polymorphs are polymorph A and polymorph X of fexofenadine hydrochloride.

NOVEL PHARMACEUTICAL COMPOSITIONS FOR ANTIHISTAMINIC-DECONGESTANT COMBINATION AND METHOD OF MAKING SUCH COMPOSITIONS

FIELD OF THE INVENTION:

The present invention relates to the pharmaceutical composition for antihistaminic-decongestant combination in the form of unit dosage form. One of the preferred embodiments of the invention is directed towards the use of novel polymorph of Fexofenadine with at least one decongestant in the form of bilayered tablet and process of making such bilayered tablets.

DESCRIPTION OF THE RELATED ART:

Antihistaminic and decongestant act by different mechanism to treat allergic reactions. Decongestants constrict vessels in the nasal mucus membranes and thereby decrease tissue swelling and nasal congestion. Decongestants are found to be better than antihistamines for restoring the potency of congested nasal airways. Histamine is a mediator released from cells, which line the walls of the nasal mucous membranes (mast cells). When released, histamine binds to local histamine receptors, thereby causing sneezing, nasal itching, swelling of the nasal membranes, and increased nasal secretions. Antihistamines relieve these effects, albeit by a different mechanism than decongestants. Antihistamines block the binding of histamines to the histamine receptors by preoccupying the histaminic receptors. Consequently they are effective only if given prior to histamine release since once histamine is released and binds to the receptors, it is too late. Although individuals typically take antihistamines after symptoms occur, it is more desirable to dose antihistamines so as to effect therapeutic availability in anticipation of histamine release.

Combining decongestants and antihistamines utilizes both mechanistic approaches, and has been shown to offer more complete relief of rhinitis symptoms than therapy with either component alone. The scientific advancement over the years has presented to the mankind the more potent and non sedating antihistamines compared to those available in old days.

U.S. Pat. No. 4,996,061 discloses the pharmaceutical composition in the form of multiple compressed tablets comprising (a) a discrete zone made with Formulation (A) which comprises a carrier base material combined with a therapeutically effective decongestant amount of a sympathomimetic drug, or a pharmaceutically acceptable salt thereof, the carrier base material being a mixture of (i) one or more pharmaceutically acceptable water-soluble nonionic cellulose ethers in an amount from about 18% to about 50% by weight of Formulation (A), (ii) one or more pharmaceutically acceptable anionic surfactants in an amount from about 2% to about 20% by weight of Formulation (A), and (iii)

one or more other pharmaceutically acceptable excipients, and (b) a discrete zone made with Formulation (B) which comprises a second carrier base material combined with a therapeutically effective antihistaminic amount of a piperidinoalkanol, or a pharmaceutically acceptable salt thereof, the second carrier base being a mixture of (i) calcium carbonate in an amount from about 0.5% to about 25% by weight of Formulation (B), (ii) one or more pharmaceutically acceptable nonionic surfactants in an amount from about 1% to about 10% by weight of Formulation (B), and (iii) one or more other pharmaceutically acceptable excipients, wherein Formulation (B) optionally also contains a therapeutically effective decongestant amount of a sympathomimetic drug, or a pharmaceutically acceptable salt thereof; with the proviso that when said pharmaceutical composition is in the form of a compression-coated tablet, the inner core zone is made with Formulation (A) and the outer coat zone is made with Formulation (B).

U.S. Pat. No.6,267,986 B1 relates to a process for the preparation of a controlled release pharmaceutical composition comprising two discrete zones wherein the first discrete zone comprises therapeutically effective amount of Pseudoephedrine or its pharmaceutically acceptable salt as active ingredient and the second discrete zone comprises a therapeutically effective amount of a long-acting antihistamine selected from the group consisting of Loratadine, Azatidine, Fexofenadine, Terfenadine, Cetirizine, Astemizole, and Levocabastine, or their pharmaceutically acceptable salt as active ingredient.

U.S. Pat. No. 6,039,974 provides a pharmaceutical composition in the form of a bilayered tablet comprising, (a) a first discrete zone made with Formulation (A) which comprises, a therapeutically effective decongestant amount of a sympathomimetic drug, or a pharmaceutically acceptable salt thereof, in an amount of about 18% to about 39% by weight of Formulation (A), and a first carrier base material, the first carrier base material comprising a mixture of; (I) carnauba wax in an amount of about 59% to about 81% by weight of Formulation (A); and (ii) a suitable antiadherent in an amount of about 0.25% to about 2.00% by weight of Formulation (A); wherein said first carrier base material provides a sustained release of the sympathomimetic drug; and (b) a second discrete zone made with Formulation (B) which comprises a therapeutically effective antihistaminic amount of a piperidinoalkanol, or a pharmaceutically acceptable salt thereof, in an amount of about 15% to about 30% by weight of Formulation (B) and a second carrier base material, the second carrier base comprising a mixture of; (I) a cellulose diluent in an amount of about 27% to about 73% by weight of Formulation (B); (ii) pregelatinized starch in an amount of about 15% to about 30% by weight of Formulation (B); (iii) a suitable disintegrant in an amount of about 0.25% to about 6.00% by weight of Formulation (B); and (iv) a suitable lubricant in an amount of about 0.25% to about 2.00% by weight

of Formulation (B); wherein said second carrier base material provides an immediate release of the piperidinoalkanol or the pharmaceutically acceptable salt thereof.

Fexofenadine is disclosed in US patent specification 3878217 and is know to have duration of action >24 hours. Pseudoephedrine and its salts are commonly administered orally three to four times a day for the relief of nasal congestion. The sustained and controlled release formulations of Pseudoephedrine are also available commercially.

Various sympathomimetic drugs, such as Pseudoephedrine, phenylephrine and phenylpropanolamine are recognized by those skilled in the art as therapeutic agents effective in the relief of nasal congestion and are commonly administered concomitantly with antihistamines for relief of nasal congestion associated with allergic rhinitis. These sympathomimetic drugs are generally effective when administered orally in unit dosage form on a four times a day dosage schedule wherein the unit dosage form provides immediate release of the active medicament. For example, the recommended dosage for Pseudoephedrine hydrochloride in adults is 60 mg every 6 hours (q.i.d.). In addition, unit dosage forms containing sympathomimetic drugs can be formulated to provide prolonged release of the active medicament so as to allow the effective daily dose to be administered on a less frequent dosage schedule. For example, the recommended dosage for Pseudoephedrine hydrochloride in a sustained release formulation can be 120 mg twice daily (b.i.d.).

Polymorphism is known phenomenon to formulation scientists. The processing of polymorphs and problems due to polymeric conversion has always been challenge to formulation scientists since ages. One of the key problems with handling of polymorphs is polymeric conversion, which affects the stability and organoleptic properties of the final product. It is well appreciated that lot of care and trials are needed to handle polymorphs in the formulation.

The present invention utilizes novel polymorph of Fexofenadine (Polymorph X or Polymorph A) to produce bilayered tablets containing at least one decongestant.

Kollidon SR is polyvinyl acetate and povidone based matrix-retarding agent. It is a white or slightly yellowish, free flowing powder. It consists of 80% polyvinyl acetate, 19% Povidone in a physical mixture. 0.8% SLS and 0.2% colloidal silica are used as a stabilizers. It is worth to mention that Kollidon SR can be successfully replaced by a mixture of polyvinyl acetate and Povidone.

Since polyvinyl acetate is plastic material that produces a coherent matrix under low compression forces, when tablets are introduced into gastric or intestinal fluid, the water-soluble povidone is leached out to form pores through which the active ingredient slowly diffuses outwards.

Kollidon SR contains no ionic groups and is therefore inert to drug substances. The Sustained release properties are unaffected by ions or salts. Kollidon SR has excellent compressibility and endows tablets with enormous hardness and low friability. This is due to the combination of the very plastic polyvinyl acetate and also the binding povidone.

It is surprisingly found that the Pseudoephedrine part of the two discrete zones of the bilayered tablets can prepared by direct compression method thus avoiding the necessity of other processes like wet granulation which involve substantially extra processing steps.

It is therefore an object of the present invention to prepare bilayered tablets containing novel polymorph of Fexofenadine with at least one decongestant.

It is another object of the present invention to use Kollidone SR in one of the layers of bilayered tablet to produce sustained release of Pseudoephedrine hydrochloride.

It is still another object of the present invention to provide a bilayered tablet comprising two discrete zones with first zone providing sustained release of the decongestant drug and second zone providing immediate release of the antihistaminic drug as used in this description.

One of the aspects of the present invention is to use direct compression technique to prepare bilayered tablet.

According to still another object, the present invention incorporates novel polymorphs of Fexofenadine which are economic as produced by eco-friendly process and has a particle size in the range of from about 12 to about 18 microns, more preferably from about 14 to about 16 microns.

The use of robust and simple manufacturing process to produce stable formulation of antihistaminic-decongestant combination to yield consistent quality product is also an object of the present invention.

SUMMARY OF THE INVENTION:

The present invention discloses the pharmaceutical composition as bilayered tablet comprising:

(a) a first discrete zone made with Formulation (A) which comprises; a therapeutically effective amount of antihistaminic drug or, a pharmaceutically accepted salt thereof in an

amount from about 10% to about 30% preferably in an amount of about 15% to about 25%, and a first carrier base material, the first carrier base material comprising, a mixture of;

(i) one or more fillers selected from cellulose derivatives in an amount from about 20% to about 45% preferably in an amount of about 30% to about 45%, starch derivatives in an amount from about 5% to about 25% preferably in an amount of about 10% to about 20%, polyols in an amount from about 10% to about 30% preferably in an amount of about 10% to about 20%, by weight of Formulation (A),

(ii) an at least one disintegrant in an amount from about 4% to about 15% preferably in an amount of about 6% to about 10%, by weight of Formulation (A),

(iii) an at least one pharmaceutically accepted glidants or lubricants in an amount from about 0.2% to about 3%, by weight of Formulation (A),

wherein, the first carrier base material provides an immediate release of the antihistaminic drug and a pharmaceutically accepted salts thereof; and

(b) a second discrete zone made with Formulation (B) which comprises; a therapeutically effective amount of a decongestant drug or, a pharmaceutically accepted salt thereof in an amount from about 20% to 40% preferably in an amount of about 25% to about 35%, and a second carrier base material, the second carrier base material comprising, a mixture of;

(i) an at least one sustained release compound in an amount from about 40% to 80% preferably in an amount of about 60% to about 75% by weight of Formulation (B),

(ii) an at least one pharmaceutically accepted glidants or lubricants in an amount from about 0.2% to about 4%, by weight of Formulation (B),

wherein, the second carrier base material provides the sustained release of decongestant drug or pharmaceutically accepted salts thereof.

The antihistaminic drugs are selected from the group consisting of novel polymorph of Fexofenadine, Loratadine, Terfenadine, Cetrizine or a pharmaceutically accepted salts thereof, preferably novel polymorph of Fexofenadine more preferably polymorph A or Formulation X of Fexofenadine. When antihistaminic drug is novel polymorph of fexofenadine the particle size of said novel polymorph of Fexofenadine is in the range of from about 12 to about 18 microns more preferably from about 14 to about 16 microns.

The Formulation (B) is made with psedoephedrine hydrochloride by direct compression method. It has been surprisingly observed that the granule size of the blend used to prepare this layer has a critical value of 5-15 % cumulative retention on mesh #80, 10-25% cumulative retention on mesh #100 and 80-95% cumulative retention on mesh #200. The said psedoephedrine granules from which second discrete layer is made of has a LOD (loss on drying) in the range of 1.5 to 3.0% preferably 2.40%.

DETAILED DESCRIPTION OF THE INVENTION

The novel polymorphs of Fexofenadine are described below.

Novel Polymorph Form A of Fexofenadine

The Form A of Fexofenadine can be identified by the following characteristics:

- a visual melting point (capillary tube) in the range of about 218-224°C;
- a melting endotherm at about 227-231°C as determined by differential scanning calorimetry;
- and an X-ray powder diffraction pattern essentially as shown in the Table1.

Table 1: XRD data of Fexofenadine Hydrochloride Form A polymorph

D-Space, Angstroms	Intensity, I/I_o, %
d value	I / Io
23.11	51
11.50	44
8.29	79
7.03	28
6.67	48
6.16	50
6.02	24
5.75	23
5.43	75
5.33	52
5.07	100
4.69	27
4.63	32
4.44	66
4.20	52
4.15	55
4.07	38
3.55	21
3.44	20

Novel Polymorph Form X of Fexofenadine

The Form X of Fexofenadine can be identified by the following characteristics:

- a visual melting point (capillary tube) in the range of about 180-188°C;
- a melting endotherm at about 184-189°C as determined by differential scanning calorimetry;
- and an X-ray powder diffraction pattern essentially as shown in the Table 2.

Table 2: XRD data of Fexofenadine Hydrochloride Form X polymorph

D-Space, Angstroms	Intensity, I/I_o, %
d value	I / Io
16.05	78
12.98	65
8.29	62
8.06	27
6.25	46

5.97	29
5.54	100
5.41	38
4.89	69
4.70	97
4.55	92
4.37	23
4.32	33
4.15	22
4.03	58
3.80	43
3.67	34
3.57	33
3.42	35

The present invention hence offers novel crystalline polymorphs of Fexofenadine and its hydrochloride and also exhibits advantages over prior art methods. Firstly, the present invention provides novel crystalline Fexofenadine, which is of high purity wherein Meta isomer of Fexofenadine is at level below 0.1 %.

Moreover, novel crystalline Fexofenadine is also prepared by a cost effective and environment friendly process, which avoids usage of mixture of solvents for recrystallization. Novel anhydrous crystalline polymorphs of Fexofenadine hydrochloride, which is obtained in almost quantitative yield from pure novel crystalline Fexofenadine. Novel anhydrous crystalline Fexofenadine hydrochloride is obtained directly from the novel crystalline Fexofenadine precursor. It is noteworthy to mention that both Fexofenadine and its hydrochloride obtained by the present invention are pure.

The details of the preparation of Fexofenadine polymorphs are described in Indian Patent Application No. 484/MAS/2001 dated June 18, 2001.

The particle size of the Form A and Form X is in the range of 12-18 microns, with not more than (NMT) 10% particles having size 5 microns, NMT 50% particles having size 20 microns, NMT 90% particles having size 50 microns. The mean particle size is 16.36 microns. The bulk density of the Fexofenadine hydrochloride polymorphs is in the range of 0.1-0.2 g/ml.

As used in this specification and in the appended claims the term "therapeutically effective amount of antihistaminic drug" means any drug selected from the group consisting of novel polymorph of Fexofenadine, Loratadine, Terfenadine, Cetrizine or a pharmaceutically accepted salts thereof, preferably novel polymorph of Fexofenadine, more preferably polymorph A or polymorph X of Fexofenadine.

As used in this specification and in the appended claims the term "therapeutically effective amount of decongestant drug" means any drug selected from the group consisting of Psedoephedrine, Phenylephrine, Phenylpropanolamine or a pharmaceutically accepted salts thereof, preferably Psedoephedrine or pharmaceutically accepted salts thereof, more preferably Pseudoephedrine hydrochloride.

It is understood that a therapeutically effective amount of antihistaminic drug is present in Formulation (A), which provides immediate release of the drug/active ingredient, and, a therapeutically effective amount of decongestant drug is present in Formulation (B), which provides sustained release of the drug/active ingredient. As used herein, the term "sustained-release" refers to a property of the pharmaceutical composition wherein the absorption and bioavailability of the active medicament is maintained in a time-release pattern such that therapeutically effective amounts of the decongestant drug are bioavailable over an extended period of time. The term "immediate-release" refers to a property of the pharmaceutical composition wherein the entire dose of active medicament is made bioavailable without substantial delay.

As used in this specification and in the appended claims the term "sustained release compound" refers to the compounds selected from the group consisting of Kollidon SR (a mixture of 80% polyvinyl acetate, 19% povidone, 0.8% SLS and 0.2% collodial silica), Sodium alginate, Xanthan gum, Carbopol, Chitosan, Ethyl cellulose, cellulose ethers, Methacrylic polymers such as Eudragit RL PO, Eudragit RS PO, and such like, which provides the sustained release of the active ingredient form the formulation. It is obvious to the person skilled in the art to replace Kollidon SR with a mixture of polyvinyl acetate and povidone. Such a mixture is also contemplated to be a substitute to Kollidon SR and are contemplated to be within the meaning of Kollidon SR in the appended claims. The active ingredient used in this specification means the one selected from decongestant and antihistaminic drugs as disclosed in this specification.

It is, of course, understood that Formulation (A) and Formulation (B) may contain any of the drug belonging to respective category as described above.

When a decongestant drug is present in Formulation (B) it is preferred that from about 10% to about 40% is present in Formulation (B), more preferably from about 25% to about 30% is present in Formulation (B). When an antihistaminic drug is present in Formulation (A) the amount depends on the drug incorporated.

As used herein and in the appended claims the term "one or more pharmaceutically accepted cellulose derivatives" refers to powdered cellulose, microcrystalline cellulose, "one or more pharmaceutically accepted starch derivatives" refers to corn starch, potato starch, starch 1500, powdered cellulose and such like. The corn starch and powdered cellulose are preferred as starch and cellulose derivatives respectively for the purpose of present invention. The disintegrants used in this specification and in the appended claims are selected from the group consisting of sodium starch glycolate, sodium carboxymethylcellulose, corsslinked polyvinylpyrrolidone, crosscarmellose sodium and such like. The preferred disintegrant as used herein includes crosscarmellose sodium. As used herein and in the appended claims the term "one or more pharmaceutically accepted excipients" refers to commonly used pharmaceutical accepted glidants or lubricants. The preferred lubricants are talc and magnesium stearate and the preferred glidants are talc and colloidal silicon dioxide. The preferred polyols are those selected from mannitol or xylitol.

As used in this specification and in the appended claims the term "suitable coating agent' means any of the commercially used tablet coating agents selected for the groups consisting of sucrose talc, precipitated calcium carbonate, gelatin, acacia, carnauba wax, etc The water soluble film-coating-material includes, for instance, various polymers such as hydroxypropylcellulose, polyethylene glycol, hydroxypropylmethylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose, etc.; a synthetic polymer such as polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [EUDRAGIT E], polyvinylpyrrolidone, a polysaccharide such as pullulan, etc.;

In a particularly preferred embodiment of the present invention, with respect to antihistaminic drug, about 60 mg of novel polymorph of Fexofenadine (Form A or Form X) or a pharmaceutically accepted salt thereof, is present in Formulation (A) and about 120 mg of psedoephedrine hydrochloride or a pharmaceutically accepted salt thereof, is present in Formulation (B).

The term Allegra-D refers to bilayered tablet commercially available by Aventis, which contains 60 mg Fexofenadine and 120 mg Pseudoephedrine hydrochloride. The term test tablet refers to the tablets prepared in accordance with the present invention.

Dosage forms containing Fexofenadine hydrochloride novel polymorphs:

The low solubility and physicochemical properties of Fexofenadine hydrochloride imposes the problem in formulation and bioavailability. Moreover, the polymeric conversion is most common still challenging aspect to the formulation scientists to ensure product quality and organoleptic properties. Therefore the selection of proper formulation technique is crucial to ensure better stability and

bioavailability of the final dosage form. Following techniques are robust enough to assure the product quality characteristic in routine manufacturing.

Bilayered tablet preparation:

The bilayered tablet of the present invention consists of two discreet layers comprising decongestant drug, Psedoepherine hydrochloride in Formulation (B) and antihistaminic drug, novel polymorph of Fexofenadine in Formulation (A). The composition and formulation of each layer is disclosed below.

EXAMPLE 1.

Step A: Formulation (A)

SN	Ingredients	Quantity mg/tablet	Percentage (%)
	Wet mass preparation		
1	Fexofenadine hydrochloride Form X or Form A	60.00	20.00 %
2	Powered cellulose (Elcema P100)	55.00	18.33 %
3	Mannitol (Pearlitol SD 200)	26.00	8.67 %
4	Corn starch B-700	23.33	7.78 %
5	Crosscarmellose Sodium	12.00	4.00 %
6	Colloidal silicon dioxide	4.50	1.5 %
8	Iron oxide	1.50	0.5%
9	Isopropyl alcohol	qs	qs
Lubrication			
10	Powered cellulose (Elcema G250)	54.00	18.00%
11	Mannitol (Pearlitol DC 400)	26.67	8.89%
12	Corn starch B-700	20.33	6.78%
13	Crosscarmellose Sodium	12.00	4.00%
14	Colloidal silicon dioxide	1.67	0.56%
15	Magnesium stearate	3.00	1.00%
	Total	300.00	100%

Sift Fexofenadine hydrochloride (Form X/A), mannitol, powdered cellulose, crosscarmellose sodium and collodial silicon dioxide through mesh #20 screen. Sift corn starch iron oxide red through mesh #80 screen. Mix the sifted material in rapid mixer granulator (RMG) for about 25 minutes. Mix the obtained dry mix from RMG with isopropyl alcohol to obtain desired wet mass. Dry the material in fluidized bed drier. Collect the mesh #24 (screen) oversize fraction after sifting the dried material and mill using 1.5 mm screen in comminuting mill. Sift powdered cellulose, mannitol and corn starch through mesh #20 screen. Colloidal silicon dioxide, crosscarmellose and magnesium stearate are sifted through mesh #40 screen. Mix the sifted and milled Fexofenadine hydrochloride material with the above sifted material in double cone blender for about 15 minutes. The dried blend is then used for compressing into tablets.

Step B: Formulation (B)

SN	Ingredients	Quantity mg/tablet	Percentage (%)
1	Pseudoephedrine hydrochloride	120	30.00%
2	Kollidon- SR	270	67.5%
3	Magnesium stearate	4.5	1.13%
4	Colloidal silicon dioxide	5.5	1.37%
	Tablet weight	400 mg	100%

Sift Pseudoephedrine hydrochloride, Kollidon SR, colloidal silicon dioxide through #60 screen. Mix all the ingredients in a suitable blender for about 20 minutes. Sift magnesium stearate through mesh #40 screen and mix with above blend in a suitable blender for about 5 minutes. The blend thus prepared is used for compression into tablets.

Step C: Tablet Compression

The granulation prepared from Formulation (A) and Formulation (B) is pressed into a suitable tablet press for preparing conventional multi layer tablets. A bilayered tablet is prepared from Formulation (B) compressed first with a hardness of 2-4 kp (Vankel) and average weight of 380-420 mg followed by compression of Formulation (A) onto the first layer resulting in tablets with an average weight of 685-715 mg and hardness of 14-20 kp.

Step D: Aqueous Coating Suspension

The tablets prepared in step (C) is coated with a transparent coat comprising of HPMC and PEG 600/Triethyl citrate dispersion prepared in purified water with about 2-3% build-up by weight resulting in tablets with average weight of 710-730 mg.

Dissolution profile of Allegra-D vs Test Tablet

The dissolution of Fexofenadine from first discrete layer and Psedoepherine hydrochloride from second discrete zone is given in following Table.

Example 1.

Apparatus: USP-I (Basket), Media: 0.001N HCL, RPM: 100 RPM.

% Drug Release												
Fexofenadine Hydrochloride (Formulation A)				**Pseudoephedrine Hydrochloride (Formulation B)**								
	15 min	**30 min**	**1 hr**		**15 min**	**30 min**	**1 hr**	**3 hrs**	**5 hrs**	**7 hrs**	**10 hrs**	**12 hrs**
Allegra -D	**86**	**93**	**101**	**Allegra -D**	**18**	**24**	**33**	**56**	**67**	**76**	**85**	**88**
Test Tablets A	**100**	**99**	**105**	**Test Tablets B**	**18**	**25**	**36**	**56**	**68**	**77**	**85**	**89**

Test Tablet A: Contains Fexofenadine Form A/X

Test Tablet B: Contains Pseudoephedrine Hydrochloride

The present invention provides a dissolution profile comparable to Allegra-D.

PHARMACOKINETIC PROFILE

When the pharmacokinetic profile of the test product is compared with that of innovator's product (Allegra –D), the pharmacokinetic parameters (AUC, Cmax, Tmax) are found to be comparable (Least square mean ratio: Test: Reference is within 80% to 125%)

The controlled drug release of Psedoephedrine hydrochloride over 12 hour post dosing has been similar in both the test and the reference formulations and the plasma concentration are above the minimum therapeutic level. (100 ng.ml)

Fexofenadine pharmacokinetic demonstrate a comparable immediate drug release profile for test and reference formulations.

In the preliminary clinical studies (Bioequivalence) there were no adverse drug reactions reported and both the formulations were without any serious side effects in the population tested. The details of the pharmacokinetic data obtained are presented below.

Pseudoephedrine hydrochloride:

	AUC $ng.hr.ml^{-1}$ (n = 12)	Cmax $ng.ml^{-1}$ (n = 12)
Test	5515.69 (35.57)	393.21 (24.75)
Allegra – D (Reference)	5164.44 (35.29)	400.51 (27.66)
Ratio of least square means (T/R) %	106.80 (38.37)	98.18 (15.30)

Fexofenadine hydrochloride:

	AUC $ng.hr.ml^{-1}$	Cmax $ng.ml^{-1}$ (n = 12)
Test	1862.27 (46.82)	300.11 (37.8)
Allegra–D (Reference)	1624.01 (66.70)	251.85 (50.2)
Ratio of least square means (T/R) %	114.67 (35.52)	119.17 (39.54)

Stability Data of Test Tablets:

The stability studies were carried out at 40°C and 75% relative humidity (40/75)

Assay

	Time			
	Initial	1 Month	2 Months	3 Months
Fexofenadine hydrochloride	110.7	103.8	103.5	113.1
Pseudoephedrine hydrochloride	97.6	94.8	94.3	93.9

Related substances

	Time			
	Initial	1 Month	2 Months	3 Months
Fexofenadine hydrochloride				
% Maximum individual Impurity	0.0602	0.0734	0.0375	0.035
% Total Impurity	0.2990	0.2965	0.2338	0.2533
Pseudoephedrine hydrochloride				
% Maximum individual Impurity	0.0509	0.0516	0.0416	.01910
% Total Impurity	0.2214	0.2314	0.2213	0.2743

Dissolution:

Fexofenadine hydrochloride	Time			
	Initial	1 Month	2 Months	3 months
60 minutes	93	97	99	100
Pseudoephedrine hydrochloride				
1 hr	37	30	28	26
2 hrs	63	49	43	42
5 hrs	79	65	56	56
12 hrs	103	90	85	90

EXAMPLE 2.

Step A: Formulation (A)

SN	Ingredients	Quantity mg/tablet
1	Fexofenadine hydrochloride Form A	60.00
2	Powered cellulose (Elcema G250)	108.00
3	Mannitol (Pearlitol DC 400)	54.00
4	Corn starch B-700	43.00
5	Colorant	1.50
6	Isopropyl alcohol	Q.S.
7	Crosscarmellose Sodium	24.00
8	Magnesium stearate	3.00
9	Colloidal silicon dioxide	6.50
	Tablet weight	300

The procedure is similar to that described in Example 1.

Step B: Formulation (B)

SN	Ingredients	Quantity mg/tablet
1	Pseudoephedrine hydrochloride	120
2	Kollidon- SR	270
3	Magnesium stearate	4.5
4	Colloidal silicon dioxide	5.5
	Tablet weight	400 mg

The procedure is similar to that described in Example 1.

The examples are explanatory only and should not be construed to limit the scope of the invention in any way. Many modifications are obvious to those skilled in the art and are contemplated to be within the scope of the appended claims.

We Claim:

1. A pharmaceutical composition as bilayered tablet comprising:

(a) a first discrete zone made with Formulation (A) which comprises; a therapeutically effective amount of antihistaminic drug or, a pharmaceutically accepted salt thereof in an amount from about 10% to about 30% preferably in an amount of about 15% to about 25%, and a first carrier base material, the first carrier base material comprising, a mixture of;

(iv) one or more fillers selected from cellulose derivatives in an amount from about 20% to about 45% preferably in an amount of about 30% to about 45%, starch derivatives in an amount from about 5% to about 25% preferably in an amount of about 10% to about 20%, polyols in an amount from about 10% to about 30% preferably in an amount of about 10% to about 20%, by weight of Formulation (A),

(v) an at least one disintegrant in an amount from about 4% to about 15% preferably in an amount of about 6% to about 10%, by weight of Formulation (A),

(vi) an at least one pharmaceutically accepted glidants or lubricants in an amount from about 0.2% to about 3%, by weight of Formulation (A),

wherein, the first carrier base material provides an immediate release of the antihistaminic drug and a pharmaceutically accepted salts thereof; and

(b) a second discrete zone made with Formulation (B) which comprises; a therapeutically effective amount of a decongestant drug or, a pharmaceutically accepted salt thereof in an amount from about 20% to 40% preferably in an amount of about 25% to about 35%, and a second carrier base material, the second carrier base material comprising, a mixture of;

(iii) an at least one sustained release compound in an amount from about 40% to 80% preferably in an amount of about 60% to about 75% by weight of Formulation (B),

(iv) an at least one pharmaceutically accepted glidants or lubricants in an amount from about 0.2% to about 4%, by weight of Formulation (B),

wherein, the second carrier base material provides the sustained release of decongestant drug or pharmaceutically accepted salts thereof.

2. The composition of claim 1 wherein:

Formulation (A) comprises;

(i) the cellulose derivatives selected from the group consisting of microcrystalline cellulose, powdered cellulose, the starch derivatives selected from the group consisting of corn starch, potato starch, pregelatinized starch, the polyols selected from the group consisting of mannitol, xylitol,

(ii) the disintegrant selected from the group consisting of crosscarmellose sodium, sodium starch glycolate, corsslinked polyvinylpyrrolidone,

(v) an at least one pharmaceutically accepted glidants or lubricants selected from any of talc, magnesium stearate or colloidal silicon dioxide, and;

Formulation (B) comprises;

(i) the sustained release compound selected from the group consisting of Kollidon SR, Ethyl cellulose, Sodium alginate, Chitosan, Carbopol, or Xanthan gum,

(ii) an at least one pharmaceutically accepted glidants or lubricants selected from talc, magnesium stearate or colloidal silicon dioxide.

3. The formulation as in any of claims 1 or 2 wherein:

(a) Formulation (A) comprises a novel crystalline Form A of Fexofenadine hydrochloride, characterized by the following X-ray powder diffraction pattern (d values in A°): 23.11, 11.50, 8.29, 7.03, 6.67, 6.16, 6.02, 5.75, 5.43, 5.33, 5.07, 4.69, 4.63, 4.44, 4.20, 4.15, 4.07, 3.55, and 3.44 and;

(b) Formulation (B) comprises Pseudoephedrine hydrochloride.

4. The formulation as in any of claims 1 or 2 wherein;

(a) Formulation (A) comprises a novel crystalline Form X of Fexofenadine hydrochloride characterized by characterized by the following X-ray powder diffraction pattern (d values in A°): 16.05, 12.98, 8.29, 8.06, 6.25, 5.97, 5.54, 5.41, 4.89, 4.70, 4.55, 4.37, 4.32, 4.15, 4.03, 3.80, 3.67, 3.57, 3.42, and;

(b) Formulation (B) comprises Pseudoephedrine hydrochloride.

5. The formulation as in any of claims 1-4 comprising, Fexofenadine hydrochloride in an amount of about 60 mg and Pseudoephedrine hydrochloride in an amount of about 120 mg.

6. The composition of claims 1 or 2 wherein;

the first carrier base material comprises powered cellulose, corn starch, mannitol, crosscarmellose sodium, magnesium stearate and colloidal silicon dioxide in an amount from about 36.33%, 14.56%, 17.56%, 8%, 1% and 2.06% respectively by weight of Formulation (A).

7. The composition of claims 1 or 2 wherein;

the second carrier base material comprises, Kollidon SR, magnesium stearate and colloidal silicon dioxide in an amount from about 67.5%, 1.125% and 1.375% respectively by weight of Formulation (B).

8. The composition as in any of claims 6 or 7 comprising;

Fexofenadine hydrochloride in an amount of about 60 mg and Pseudoephedrine hydrochloride in an amount of about 120 mg.

9. The composition of claims 1 or 2 wherein, formulation (A) comprises, the antihistaminic drug is selected from any of the group consisting of Loratadine, Terfenadine, Cetrizine or a pharmaceutically accepted salts thereof.

10. A method of making bilayered tablet according to claim 1 comprising the steps of:

performing the operation in two separate steps comprising step (A) and step (B),

wherein step (A) comprises;

(i) sifting of Fexofenadine hydrochloride, powdered cellulose, mannitol, crosscarmellose sodium and colloidal silicon dioxide through #20 screen, sifting of corn starch and iron oxide red through mesh #80 screen,

(ii) mixing the content of step (i) in rapid mixer granulator for about 25 minutes,

(iii) mixing the content of step (ii) with isopropyl alcohol to obtain wet mass,

(iv) drying the content of step (iii) in fluidized bed dryer followed by sifting and milling using a mechanical sifter and a comminuting mill, the comminuting mill comprising a screen of 1.5 mm, and;

(v) alternatively sifting powdered cellulose, mannitol, corn starch, colloidal silicon dioxide and crosscarmellose through 20 # screen, sifting of colloidal silicon dioxide and crosscarmellose through mesh #40,

(vi) mixing the dried content of step (iv) with the content of step (v) in double cone blender for about 10 minutes,

(vii) sifting magnesium stearate through mesh # 40 screen and mixing with the content of step (vi) in suitable blender for about 5 minutes;

wherein, step (B) comprises;

(i) sifting of Pseudoephedrine hydrochloride, Kollidon SR and colloidal silicon dioxide through #40 screen,

(ii) mixing the content of step (i) in suitable blender for about 20 minutes,

(iii) sifting of magnesium stearate through mesh #40 screen, mixing said sifted magnesium stearate with content of step (ii) in suitable blender for about 5 minutes, and;

compressing the material of step (A) and step (B) into tablets.

11. The method of claim 10 wherein:

step (A) comprises;

Fexofenadine hydrochloride Form A, mannitol, powdered cellulose, corn starch, colloidal silicon dioxide in an amount of about 60mg, 54mg, 108 mg, 43mg and 6.5mg respectively by weight of formulation (A).

wherein, step (B) comprises;

Pseudoephedrine hydrochloride, Kollidon, colloidal silicon dioxide and magnesium stearate in an amount of about 120mg, 270mg, 5.5mg, 4.5mg respectively by weight of formulation (B).

12. The method of claim 10 wherein:

step (A) comprises;

Fexofenadine hydrochloride Form X, mannitol, powdered cellulose, corn starch, colloidal silicon dioxide in an amount of about 60mg, 54mg, 108 mg, 43mg and 6.5mg respectively by weight of formulation (A).

wherein, step (B) comprises;

Pseudoephedrine hydrochloride, Kollidon, colloidal silicon dioxide and magnesium stearate in an amount of about 120mg, 270mg, 5.5mg, 4.5mg respectively by weight of formulation (B).

13. The formulation of claim 12 wherein, the bilayered tablet is coated with the suitable coating agents.

14. The formulation of any of claims 1-11 as bilayered tablet.

15. The formulation of claim 14 wherein, the bilayered tablet is coated with the suitable coating agents.

16. The formulation as in any of claims 12-15 wherein bilayered tablet is prepared by direct compression technique.

17. A method of treating mammalian animal in need of such a treatment using the composition of any of claims 1-14.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 02/01068

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/495 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 267 986 B1 (JAIN GIRISH KUMAR ET AL) 31 July 2001 (2001-07-31) cited in the application column 2, line 44 - line 61 column 5 -column 10; examples	1,9,14, 16,17
X	US 4 996 061 A (WEBB NORVAL E ET AL) 26 February 1991 (1991-02-26) cited in the application column 1, line 29 - line 48 column 3, line 52 -column 4, line 40 examples column 7, line 33 - line 41 claims	1,14,16, 17
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2002	25/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Rankin, R

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/01068

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Interna[redacted]al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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T	WO 02 080857 A (DOLITZKY BEN-ZION ;GROSS IRWIN (IL); TEVA PHARMA (IL); WIZEL SHLOM) 17 October 2002 (2002-10-17) page 3 -page 6 page 26 -page 37; examples	1-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/01068

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 17

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/IB 02/01068

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